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OBSERVATIONS ON

THE EXCRETION OF URIC ACID IN HEALTH AND DISEASE.*

By C. A. HERTER, M. D., and E. E. SMITH, Ph. D.,†
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The study of the end-products of nitrogenous metabolism, urea and uric acid, through which nitrogen is excreted from the body, has for a long time occupied the attention of investigators and to a less extent that of practicing physicians. The practitioner has concerned himself especially with the question of uric-acid excretion in its relation to disease, but the usefulness of his observations has usually been impaired, even for clinical purposes, by a very serious deficiency. This is that he has not had at his command any method of estimating, with even reasonable accuracy, the amount of uric acid in a specimen of urine. The presence of a considerable number of uric-acid crystals in the sediment of a urine has commonly been regarded as evidence of excessive uric-acid excretion. The important fact has been overlooked that the separation of uric-acid crystals or of

* Read before the New York Neurological Society, May 3, 1892.

† The determination of uric acid, and the chemical work generally, have been done by Mr. Smith at my request.—C. A. H.

urates depends more on the degree of concentration of the urine and its acidity than on the presence of uric acid in excess. In other words, such separation does not necessarily depend on an excess of uric acid. Nor, on the other hand, does the non-deposition of uric acid constitute evidence that a urine does not contain uric acid in excess. We do not wish to be understood that the separation of crystals of uric acid from the urine has no significance. Such a separation is more likely to occur when uric acid is in excess than when it is not, and when it occurs in the course of a few hours in a urine of which the specific gravity is less than 1·025 may perhaps be regarded as creating a presumption that there is an excess. The use, however, of such a criterion as this is responsible for many erroneous statements.

But supposing that the methods at the command of the physician could give him a reasonably accurate knowledge of the amount of uric acid present in a given urine, he would still be somewhat in the dark as to the significance of the result unless he was conversant with the variations in uric-acid excretion that occur in health. We propose in this paper to show what these variations are and upon what they depend, with a view to establishing a criterion for the use of those who wish to know the state of uric-acid excretion in special cases. We shall endeavor to point out especially the following facts :

First. That the absolute quantity of uric acid excreted varies chiefly with the character of the diet, being high on a highly nitrogenous diet and low on a diet of carbohydrates principally. In health the quantity of urea excreted depends on the quantity of nitrogenous food ingested. Hence in health both urea and uric acid totals vary widely with the quality and quantity of the food.

Second. That the chief clinical criterion as to whether

uric-acid excretion is normal, is not the absolute amount of uric acid excreted, but the ratio of the uric acid to the urea excreted.

Third. That the ratio of uric acid to urea in the twenty-four hours' urine from the same individual in health is fairly constant.

Fourth. That this ratio is not so constant for different individuals at different periods of life, but varies between 1 to 45 and 1 to 75.

We shall give the facts from which these conclusions have been reached. They are derived largely from original observation. In many respects our results merely confirm and extend those of other workers. We shall, however, call attention to certain facts regarding deviations from normal uric-acid excretion which, so far as we are aware, have been hitherto unnoted.

It is not easy to present the facts we wish to touch upon in simple and logical order. It is convenient to consider them under the following heads:

1. The Methods used in determining Uric Acid and Urea.

2. The Variations in Total Uric-acid Excretion under the Influence of Diet, Exercise, etc.

3. The Variations in Total Urea Excretion under the Influence of Diet, Exercise, etc.

4. The Quantitative Relation of Uric Acid and Urea in Health.

5. The Excretion of Uric Acid as influenced by Drugs.

6. The Excretion of Uric Acid in Disease.

1. The Methods used in determining Uric Acid and Urea.

It is exceedingly important that we should mention briefly the methods employed in our work, since the char-

acter of the results and the reliance to be placed on them depends largely on correct methods. The error in much of the work that has been done on uric-acid excretion is due to the use of inaccurate methods of determining uric acid.

Of the numerous methods used in determining uric acid, that known as the Ludwig-Salkowski * method is undoubtedly deserving of the greatest confidence and is the one employed by us. It is a gravimetric method of great accuracy.† The drawbacks to it are the number of manipulations involved and the fact that it usually takes several days to get a result. It is not adapted for clinical work, and, unfortunately, there is as yet no method which is.

It is customary to calculate the urea of the urine from

* A good description of this method can be found in the last edition of Neubauer's and Vogel's work on the urine. The following modification of the method is employed by us: 200 c. c. of urine are treated with 20 c. c. each of the standard magnesian mixture and silver-nitrate solution, after the usual manner. With concentrated urine, of from 1·022 sp. gr. and upward, especially where highly colored, it is more satisfactory to take only 100 c. c., using 20 c. c. each of the standard solutions as before. After filtering and washing with ammoniacal water, the precipitate of phosphates and silver urate is removed from the filter paper into the beaker by the aid of a stream from the wash bottle, the paper being retained for subsequent filtration. Instead of using sodium sulphide for decomposing the silver urate, we employ a solution of potassium iodide, as suggested by Graves (*Jour. of Phys.*, 12, 1891). Occasionally, however, silver iodide appears in the filtrate, in which case it is necessary to redissolve the separated uric acid in weak sodium hydroxide and filter hot, when the urate is obtained in solution quite free from weighable traces of silver. For weighing, filter papers of 7 ctm. diameter are employed, which are dried and weighed in small weighing bottles. The crystals are washed with about 30 c. c. of water and the usual correction for dissolved uric acid added to the weight actually found.—E. E. S.

† Ludwig recovered about ninety-eight per cent. of uric acid from pure solutions. Two parallels on the same urine gave us 0·390 gramme and 0·382 gramme for the twenty-four hours.

its total nitrogen content. This is accomplished either directly by the Kjeldahl process or the well-known hypobromide method, or, indirectly, by Liebig's urea method. The method used by us is Pflüger's modification of Liebig's method,* a volumetric process that has been well indorsed for clinical and research work. Among its advantages are its ready applicability and the relatively simple apparatus required. The method, however, only approximates a urea method, since other nitrogenous substances which are contained in the urine are estimated as urea. The chief of these are uric acid, creatin, creatinin, xanthin, and other extractives. These substances are contained in the urine in amounts that are small as compared with urea, but they make the results on urea determinations higher than they should be. We shall return to this point.

But while the Liebig method approximates a total nitrogen method, it differs from it in one important respect—namely, this: that it does not include the nitrogen of the ammonium salts. These are present normally in only small amount, but when administered for therapeutic purposes they appear in the urine in increased quantity, and hence increase the nitrogen as estimated from the total nitrogen present. On the other hand, the use of salicylates in large amounts leads to an overestimation of the urea as determined by the Liebig method, since the salicyluric acid that appears in the urine is precipitated as urea.

2. The Variations in Total Uric-acid Excretion under the Influence of Diet, Exercise, etc.

Uric acid is the medium by which in man the largest amount of nitrogen, next that eliminated as urea, is excreted from the body. Recent investigations have made it

* The chlorides are removed with a standard solution of silver nitrate.

probable that uric acid is formed chiefly in the liver and spleen; there appears to be no satisfactory evidence that it is formed in the kidney. The most interesting work that has been done on the source of uric-acid production is that of Schröder * and Minkowski.† Schröder found that after the removal of the kidneys in birds uric acid continues to be formed and accumulates both in the blood and liver. He found, further, that the quantity of uric acid in the liver could be greatly increased after the removal of that organ from the body by passing blood through it.

Minkowski's results confirmed those of Schröder. This observer removed the liver from geese and studied the effect of this removal upon the urine. He found that the urine, instead of containing sixty or seventy per cent. of uric acid, as it normally does, contained only two or three per cent. Coincident with this fall in uric acid there was a great increase in the amount of ammonia. Furthermore, the urine contained lactic acid. Minkowski thinks it probable from these facts that the liver is the chief agent in the formation of uric acid, and suggests that uric acid may be derived in the liver by the synthesis of lactic acid and ammonia.

The quantity of uric acid excreted daily by a normal adult varies considerably, and this variation depends more upon the character of the diet than upon any other factor. A highly nitrogenous diet increases the excretion of uric acid. A diet poor in nitrogen greatly diminishes it. A healthy man weighing one hundred and fifty pounds usually excretes between seven and ten grains (0·5 and 0·75 gramme) of uric acid daily. But it is a very important fact, and one which we wish to emphasize particularly, that the mere total quantity of uric acid in the twenty-four hours' urine

* Ludwig's *Festschrift*, 1887, p. 89.

† *Archiv f. experimentelle Pharmakologie und Pathologie*, xxi.

gives no knowledge as to whether this quantity is or is not excessive. In order to obtain this knowledge it is essential that we should know what is the total quantity of urea (or the total nitrogen) excreted during the twenty-four hours in which the uric acid is estimated. We shall refer to this point again.

Exercise increases somewhat the quantity of uric acid excreted, but the influence even of vigorous and prolonged exercise is inconsiderable. The differences in uric-acid excretion at different ages are not exactly proportioned to the body weight of the individual. Thus, from the second year of life to the time of puberty the quantity of uric acid contained in the urine is distinctly greater in proportion to the body weight than in adults. This is due apparently to the greater relative assimilation of nitrogenous food at this period of life. It is said that during the first year of life the uric-acid excretion is more nearly proportioned to the body weight.

3. The Variations in the Total Urea Excretion as influenced by Diet, Exercise, etc.

Urea is thechief end product of nitrogenous metabolism. Probably nearly ninety per cent.* of the nitrogen that leaves the body is in the form of urea. Of course, the urea in the urine is not derived directly from the food taken into the body; it is necessary that the food should be first assimilated and its nitrogen become part of the tissues of the body before the ingested nitrogen enters into the formation of urea. Nevertheless, the quantity of urea excreted is, in a general way, proportioned to the amount of nitrogenous food assimilated. This is a most important fact, for it thus happens that the quantity of urea excreted is an

* Camerer gives this figure. See *Zeitschrift f. Biologie*, xxiv, p. 306. Other observers give somewhat lower figures.

index of the activity of the nitrogenous metabolism of the body. If an adult (of 150 pounds weight) is regularly excreting a large amount of urea daily,* say 50 grammes or thereabouts, this is good evidence that there is extensive tissue waste, and if the individual is not losing weight we know that he must be assimilating a large amount of nitrogenous food. If, on the other hand, he is excreting a small amount of urea daily, say 12 or 15 grammes, it is safe to infer that a small amount of nitrogenous food is being assimilated, provided the weight is reasonably constant.

The influence of food on urea is well illustrated by the following observation: A man weighing 170 pounds, in good general health, and who was somewhat cautious about the use of nitrogenous food, passed in five consecutive days the following amounts of urea daily: 21·490, 22·591, 19·514, 19·649, and 19·989 grammes. He was then put upon a highly nitrogenous diet and the urea excretion jumped at once to the following figures: 28·701, 29·076, 19·799, 29·350, 37·268, 39·731, 41·203, 39·161, 38·126, 41·392, and 36·602 grammes. The subject returning to a less liberal nitrogenous diet, the urea fell at once to the following figures: 27·795, 29·191, 24·143, 23·034, 24·292, 26·549, 25·085, 23·150, 24·901, 22·362 grammes.

It is thus plain that the quantity of proteids ingested is the great factor in determining the amount of urea excreted. Other influences are of relatively little importance. Exercise, which was once thought to exert an important influence in increasing the urea elimination, has been

* A normal man weighing 150 pounds and varying only slightly in weight excretes from 25 to 40 grammes of urea per day if he is on a mixed diet—*i. e.*, his urea averages somewhere in the neighborhood of one ounce.

shown to have little effect. The observations of Voit * on a dog made to turn a tread-mill, and those of Fick and Wislicenus † in the ascent of the Faulhorn, are well known. More recently Parkes,‡ experimenting on soldiers, and North,# experimenting on himself, have shown that the increase of urea from exercise is exceedingly small as compared with the loss of body weight or the work done.

What has been said of the disproportionately large excretion of uric acid in childhood is true also of the excretion of urea. Thus reference to Table I will show that a child eighteen months old, and weighing twenty-eight pounds, excreted about 12 grammes of urea per day, while a child ten years old, and weighing one hundred pounds, excreted regularly between 25 and 30 grammes. This relatively greater excretion of urea in childhood than in adult life depends probably on the more active metabolism of child life.

We have already spoken of the importance of using the urea excretion as a standard in deciding whether the excretion of uric acid is normal or abnormal. We may now pass to a more minute examination of the quantitative relation of uric acid and urea in health, and subsequently to their relation under the influence of drugs and in disease.

4. The Quantitative Relation of Uric Acid and Urea in Health.

We have stated that the quantity of uric acid excreted by a normal individual depends chiefly on the character of the diet, and we have stated that the quantity of urea ex-

* *Untersuch. über der Einfluss des Kochsalzes, des Kaffees und der Muskelbewegungen auf der Stoffwechsel.* Munich, 1860.

† *Vierteljahresschrift d. naturf. Gesellsch. in Zürich*, 1865.

‡ *Proceedings of the Royal Society*, xi, 339.

Journal of Physiology, i, 171.

creted depends chiefly on the same factor. If we increase the assimilation of nitrogenous food beyond the average required, there is an increase both of uric acid and urea in the urine, and this increase in the two end-products is in a general way proportional. According to some observers, the uric-acid excretion increases a little more rapidly than the urea excretion. Other observers have found the urea output to increase a little faster, proportionally, than that of the uric acid, when nitrogenous food is increased. Our experience, so far as it goes, confirms the latter view, but it is possible that more extended observation would show that no general statement can be made as to this point.

The quantity of nitrogenous food assimilated by an individual in health who lives on a mixed diet and leads a reasonably regular life, of course varies a little from day to day, but not enough to cause a wide variation in the quantitative relation of uric acid and urea in the urine.* We have analyzed the twenty-four-hour urines of a considerable number of persons, and have found the relation between uric acid and urea to be fairly constant from day to day, even though no effort was made to keep the quantity of nitrogenous food daily ingested even approximately the same. Reference to Table I will illustrate the truth of this statement.

But, while the relationship between uric acid and urea is thus fairly constant in the same individual, there is a much more considerable variation among different individuals of the same and different ages. It is difficult to give figures stating what is the average relation in health. We may say that in our experience the relation varies between 1 to 45 and 1 to 65 in adults. A relation higher

* Of course, twenty-four-hour samples of urine must be used for comparison. It is also desirable that the patient should take little or no alcohol during the period of observation.

than 1 to 45 we look upon with suspicion, unless it is known that it is a habitual relation, and that the individual is in good health. A relation lower than 1 to 70 is probably not met with in normal adults on a mixed diet. On a bread or milk diet, however, the relation may easily run as low as 1 to 80, or even lower, in health. Thus, Bunge * mentions the case of a young man whose urine showed a relation of 1 to 48 while he was on a meat diet, and a relation of 1 to 82 while he was on a diet of bread. In one case of *petit mal* the relation of uric acid and urea ran as follows on a mixed diet: 1 to 32·5, 1 to 36·8, 1 to 39·2, 1 to 43·2, 1 to 39·2. On an exclusively milk diet the relations ran as follows: 1 to 61·4, 1 to 66·1, 1 to 76·5, and 1 to 85·8. The absolute reduction in the excretion of uric acid was in this case even more striking than the relative reduction, for the total excretion of urea was distinctly reduced by the milk diet.

TABLE I.

Showing the Ratio of Uric Acid and Urea in Health.

No.	Age.	Weight.	Sp. gr.	Volume.	NaCl.	P_2O_5.	Urea.	Uric acid.	Ratio.
		Pounds.		C. c.	Grammes.	Grm.	Grammes.	Grm.	
1	12 mos.	22	1·010	244	·69	·4045	3·701	·0696	1 : 53·9
"	19 "	28	1·017	470	.....	1·166	12·095	·206	1 : 55·7
"	19 "	"	1·014	685	.....	1·099	11·508	·207	1 : 55·5
2	2½ yrs.	33	1·028	375	.....	.....	4·437	·141	1 : 81·1
3	3 "	36	1·022	580	.....	.....	12·702	·166	1 : 76·5
4	4 "	40	1·013	615	3·268	·6815	12·979	·1752	1 : 74
5	4½ "	39	1·021	510	.....	.....	12·495	·200	1 : 62·4
6	5 "	43	1·019	715	.....	1·736	16·016	·208	1 : 77
7	6 "	45	1·024	450	.....	1·591	17·55	·259	1 : 67·7
8	6½ "	50	1·027	765	.....	2·681	25·245	·328	1 : 76·9
9	7 "	55	1·024	530	5·754	1·028	13·606	·251	1 : 54·2
"	7 "	"	1·021	540	4·247	1·026	15·040	·282	1 : 53·1
10	8 "	60	1·016	1,065	6·854	1·271	21·244	·396	1 : 54·1
11	10 "	74	1·015	1,385	5·674	1·888	31·294	·418	1 : 74·6
"	10 "	"	1·010	1,300	.....	.....	25·410	·351	1 : 72·4
12	12 "	76	1·024	695	.....	1·906	24·116	·398	1 : 60·6

* *Lehrbuch d. physiolog. Chemie*, 1889.

No.	Age.	Weight.	Sp. gr.	Volume.	NaCl.	P_2O_5.	Urea.	Uric acid.	Ratio.
		Pounds.		C. c.	Grammes.	Grm.	Grammes.	Grm.	
13	12 yrs.	76	.....	....	.....	.....	19·904	·329	1 : 60·5
14	15 "	150 (?)	1·028	825	.....	2·086	25·905	·465	1 : 55·7
15	19 "	"	1·021	600	5·838	1·211	12·230	·226	1 : 54
16	21 "	150	1·022	1,195	.....	2·330	30·233	·424	1 : 71·3
"	21 "	"	1·020	1,780	.....	.....	38·445	·587	1 : 65·5
17	21 "	190	1·027	965	.....	.....	31·555	·595	1 : 52·6
"	21 "	"	1·025	1,370	.....	.....	37·401	·682	1 : 54·9
"	21 "	"	1·018	1,640	.....	.....	34·768	·657	1 : 52·9
"	21 "	"	1·020	1,485	.....	.....	32·224	·643	1 : 50·1
18*	21 "	141	1·016	1,280	.....	.....	33·380	·749	1 : 44·30
"	21 "	"	1·017	1,200	.....	.....	30·486	·708	1 : 47·29
"	21 "	"	1·014	1,340	.....	.....	33·947	·739	1 : 45·82
"	21 "	"	1·018	1,030	.....	.....	33·058	·753	1 : 45·21
"	21 "	"	1·017	1,150	.....	.....	34·502	·779	1 : 44·28
"	21 "	"	1·015	1,250	.....	.....	32·619	·723	1 : 45·13
"	21 "	"	1·023	880	.....	.....	33·440	·741	1 : 45·11
"	21 "	"	1·013	1,590	.....	....	34·370	·694	1 : 49·52
"	21 "	"	1·016	1,250	.....	.....	33·334	·777	1 : 42·98
19	24 "	160	1·031	1,035	12·398	2·317	25·890	·446	1 : 58
"	24 "	"	1·029	1,000	.....	.....	27·805	·490	1 : 56
"	24 "	"	1·030	895	.....	.....	23·244	·462	1 : 50·3
"	24 "	"	1·031	710	.....	.....	30·569	·514	1 : 59·4
"	24 "	"	1·030	635	.....	.....	26·218	·482	1 : 54·3
"	24 "	"	1·029	800	.....	. ..	28·538	·540	1 : 52·8
"	24 "	"	1·028	755	.....	.....	22·692	·448	1 : 50·5
20	24 "	90	1·019	660	.....	.....	11·748	·258	1 : 45·5
21	25 "	145	1·024	1,585	20·456	3·312	42·671	·789	1 : 54
"	25 "	"	1·028	840	9·980	2·239	28·59	·549	1 : 52
22	26 "	...	1·026	955	11·525	2·774	38·82	·738	1 : 54
"	26 "	...	.....	....	.....	.....	39·88	·715	1 : 55·7
23	27 "	160	.....	.....	.....	. ...	27·30	·620	1 : 44·1
"	27 "	"	.....	....	.....	.....	32·95	·740	1 : 44·5
24	28 "	130	1·017	1,970	.....	1·741	27·97	·329	1 : 52·8
"	28 "	"	1·022	2,880	18·27	2·436	35·74	·764	1 : 46·8
25	30 "	103	... .	.....	4·785	1·211	12·77	·246	1 : 51·9
27	53 "	165	1·020	1,045	.....	2·070	27·06	·509	1 : 53·1
28	57 "	170	1·023	1,130	11·69	1 956	25·38	·489	1 : 51·9
29	74 "	104	1·026	420	.....	.....	11·55	·215	1 : 53·7
"	74 "	"	1·020	500	.....	.....	12·010	·253	1 : 47·4

It will be noted on examining the table that there is apparently little difference in the quantitative relation of the

* The figures from this case are taken from Chittenden and Taylor. *Studies from the Laboratory of Physiological Chemistry* (Yale), 1889.

two end products at different times of life. Upon the whole it would appear that in children the average ratio is a little lower normally than in adults, but our observations are not sufficiently numerous to enable a definite conclusion to be drawn as to this point.

Newly born children are an exception to the general equality that holds for different periods of life.* It has been shown that during the first few days of life the relation of uric acid to total nitrogen excretion is much higher than at any other period; but this exception is of no practical interest to us.

We have, then, in the quantitative relation between uric acid and urea a standard of practical utility by which it is possible to determine with confidence the state of uric-acid excretion. It is of course essential that twenty-four-hour samples be used, for the ratio between the two substances varies at different times of day, and a partial sample may not be a reliable index to the condition of the twenty-four hours' uric-acid excretion.† Thus, a partial sample taken two or three hours after a meal rich in nitrogen might show a suspiciously high relation—say, 1 to 40—whereas the twenty-four hours' urine from the same individual might show a relation of 1 to 50, which would be, presumably, normal.

The variations that occur in health in the relation of uric acid and urea at different periods of the day have not been studied so carefully as could be wished. Camerer ‡ has shown that, after a meal rich in nitrogen, the uric-acid excretion is at its highest during the hours immediately after the meal, while the excretion of urea is at its highest

* See Martin, Ruge, and Biedermann, *Ctrlbl. f. d. m. Wissenschaften*, 1875, p. 387. See, also, Hofmeier (Virch. *Arch.*, 89, p. 493).

† *Zeitschrift f. Biologie*, 1889, 26 (p. 109).

‡ *Ibid.*

eight or nine hours after the meal. But Camerer's observations were made in cases where only one nitrogenous meal was taken in the twenty-four hours, and these cases did not conform in this and other respects with ordinary conditions.

It is necessary that we should say a word about the figures given in our table. As already stated, the Liebig method of determining urea is not, strictly speaking, a urea method; it is more nearly a total nitrogen method. Hence the ratios given in the table are lower than they would have been if obtained by the use of an ideal urea method. According to Camerer,* about ninety per cent. of all the nitrogen the urine contains is present as urea; according to Bohland,† the amount is smaller, being about eighty-five per cent. of the total nitrogen. We might therefore have corrected our figures by the subtraction of ten or fifteen per cent. from the figures which we give for urea, but have preferred to give our first figures for what they are, and allow others to make a correction of this kind if they wish.

Haig ‡ follows Garrod in giving 1 to 33 as the relation of uric acid to urea in health. There is thus a wide discrepancy between this ratio and the limits in health as given by us—namely, 1 to 45 to 1 to 65. This difference is not to be accounted for by the facts mentioned in regard to the urea method we have employed, since, even with the correction above suggested, there is still a wide difference between the figures. Moreover, the urea method used by Haig is open to precisely the same objection as that used by us. There can be little doubt that the reason for Haig's high figure is that the method used by him for determin-

* *Loc. cit.*

† Pflüger's *Archiv*, xliii.

‡ *Brain*, 1891. This view seems to be based chiefly on one case. See also *Journal of Physiology*, vol. viii, 1887.

ing uric acid (Haycraft's method) is faulty and regularly gives high results. This is conclusively shown by Herringham and Groves* in a recent paper. We have no hesitation in stating that a relation of 1 to 33 in a twenty-four-hour sample of urine is pathological. The ratios given by us for health correspond closely with the figures of Bunge, Vogel, Salkowski, and Pfeiffer.

5. The Excretion of Uric Acid as influenced by Drugs.

From a practical point of view, no observations on the excretion of uric acid are of more interest than those which relate to the effect of drugs. Observations have been made upon the action of a variety of drugs, and in some instances conclusions have been reached that may be regarded as definitive; but much that has been written is of little or no value, owing to the inaccuracy of methods used in determining uric acid, or to more or less glaring defects in the conditions under which the experimental work has been done. In the case of some drugs there are conflicting opinions as to their influence upon the elimination of uric acid. We shall touch briefly upon the results of the work which, in our estimation, is most to be trusted. We may conveniently consider, first, the drugs that are supposed to increase the excretion of uric acid, and, secondly, those that are supposed to diminish it.

Alcohol.—As to the effect of moderate doses of alcohol upon uric-acid excretion the evidence is conflicting. According to von Jaksch, alcohol, in other forms than beer and wine, diminishes the excretion both of uric acid and urea. We have made some observations which bear on this

* Herringham and Groves. *Journal of Physiology*, 12, 1891. These observers used the Ludwig-Salkowski method, but their normals give much wider variations than do ours.

question. A healthy young man, weighing one hundred and ninety pounds, was given whisky in increasing doses for three days. The first day the quantity taken was two ounces; the second day, three ounces and a half; the third day, six ounces. The urine was examined before and after the trial. The results are shown in the table:

TABLE II.

Showing Influence of Whisky upon Uric-acid Excretion.

			Relation of uric acid to urea.
First day before experiment, no alcohol	Urea,	31·555 grm.	1 : 52·6
	Uric acid,	·599 "	
Second day before experiment, no alcohol	Urea,	37·401 grm.	1 : 54·9
	Uric acid,	·682 "	
Third day before experiment, moderate use of beer and champagne	Urea,	29·052 grm.	1 : 48·3
	Uric acid,	·601 "	
First day on whisky, 2 oz.	Urea,	36·425 grm.	1 : 52·2
	Uric acid,	·697 "	
Second day on whisky, 3½ oz.	Urea,	33·534 grm.	1 : 54
	Uric acid,	·620 "	
Third day on whisky, 6 oz.	Urea,	33·460 grm.	1 : 53·1
	Uric acid,	·630 "	
First day after experiment, no alcohol	Urea,	34·768 grm.	1 : 52·9
	Uric acid,	·657 "	
Second day after experiment, no alcohol	Urea,	32·768 grm.	1 : 50·1
	Uric acid,	·643 "	

Inspection of this table makes it evident that in this case the whisky taken exerted no appreciable effect upon the excretion of uric acid. The relations between uric acid and urea on the days when whisky was taken coincides with those of the days before and after, when no alcohol was taken. The slight change in ratio on the day before the use of whisky was begun may have been due to the use of beer and champagne on that day. With a view to seeing whether the influence of champagne (in quantities containing alcohol in amount approximately equivalent to that contained in the whisky) differed from

that of whisky, another observation was made. The subject was given champagne in increasing amounts for three days. On the first day the quantity taken was eight ounces; on the second, sixteen ounces; on the third, twenty-four ounces. The results are shown in the table:

TABLE III.

Showing Influence of Champagne on Uric-acid Excretion.

		Ratio of uric acid to urea.
First day, 8 oz. champagne.....	Urea, 31·699 grm. Uric acid, ·754 "	1 : 42
Second day, 16 oz. champagne..	Urea, 29·758 grm. Uric acid, ·655 "	1 : 45·1
Third day, 24 oz. champagne...	Urea, 32·172 grm. Uric acid, ·686 "	1 : 46·8
Fourth day, no alcohol.....	Urea, 32·947 grm. Uric acid, ·643 "	1 : 51·2

It is evident from these figures that while whisky had no effect upon the ratio of uric acid and urea, champagne in quantities containing an equivalent of alcohol caused a decided deviation from the habitual ratio owing to an increase in uric acid. It is interesting to note that the ratio returned at once to the habitual on the discontinuance of the wine. A single observation like this proves nothing, but is not without suggestiveness.

There is good reason to believe that doses of alcohol which in health cause no effect upon the excretion of uric acid, increase this consi lerably and disturb the normal relation to urea in persons with the uric-acid diathesis—*i. e.*, in persons who tend habitually to excrete uric acid in excess.

The best work that has been done upon the influence of large doses of alcohol is that of Chittenden and Smith,* whose observations were on dogs in a state of nitrogenous

* The Influence of Alcohol on Proteid Metabolism. *Journal of Physiology*, vol. xii, No. 3, 1891.

equilibrium. There is no doubt as to the effect, at least in dogs, of the doses employed by these observers. While the total excretion of nitrogen was somewhat diminished, the elimination of uric acid was greatly increased, the increase amounting to about one hundred per cent.

Sodium Salicylate.—There has been some difference of opinion as to the effect of this drug, but recent observers agree that salicylate of sodium causes a decided increase in uric-acid excretion as compared with urea. We have made the following observations on this drug: A young man in good health was given three grammes of sodium salicylate three times daily for three days. The urine was studied on these days, and on the day before and the day after. The results are given in Table IV.

TABLE IV.

Showing Influence of Sodium Salicylate upon Uric Acid.

		Ratio of uric acid to urea.
Day before salicylate	Urea, 26·458 grm. Uric acid, ·478 "	1 : 55·3
First day on salicylate, 3 grm. taken	Urea, 26·684 grm. Uric acid, ·555 "	1 : 48·1
Second day on salicylate, 3 grm. taken	Urea, 31·420 grm. Uric acid, ·615 "	1 : 51·1
Third day on salicylate, 3 grm. taken	Urea, 27·784 grm. Uric acid, ·730 "	1 : 38
Day after salicylate	Urea, 27·805 grm. Uric acid, ·490 "	1 : 56

In this case the effect of the salicylate of sodium was decided. The increase in uric acid was greatest on the third day of the trial, when the ratio to urea was 1 to 38. On the day after this the relation went back to 1 to 56—that is, to about where it was on the day before the salicylate of sodium was first taken.

Two similar observations were made upon persons who are subject to migraine. In the first case five grains of

salicylate of sodium, t. i. d., were taken for three days. After this, ten grains, t. i. d., were taken for three days. The results were quite inconclusive. In the second case the quantity taken was three grammes daily for three days. The results in this case were also inconclusive. It is interesting that in both cases the use of the drug was accompanied by headache, which in the first case lasted several days and was general in distribution; and in the second case was a typical migraine paroxysm coming on at the end of the experiment.

Alkalies.—Alkaline waters are said by some to increase and by others to decrease the excretion of uric acid. Which of these views is correct we are unable to say. The question appears to call for reinvestigation.

Quinine.—In recent times the influence of quinine upon metabolism has been studied by Kerner,* Prior, † and Sassetzky. ‡ Kerner found that doses of 9·3 grains of quinine hydrochloride, continued for three days, reduced very considerably the excretion both of urea and uric acid. But while urea was decreased twelve per cent., uric acid was decreased fifty-four per cent. These small doses of quinine, therefore, greatly diminished uric-acid excretion, both absolutely and relatively. The experiments of Prior gave equally striking results as regards the diminution of uric-acid elimination, and Sassetzky, experimenting with fever patients, was able to confirm Kerner's observations.

Kerner's results have been criticised by Oppenheim,# who found that a dose of 30·8 grains of quinine increased

* Pflüger's *Archiv*, vol. iii, p. 104.

† Ueber den Einfluss des Chinin auf den Stoffwechsel des gesunden Organismus. Pflüger's *Archiv*, vol. xxiv, p. 237.

‡ Ueber den Einfluss fieberhafte Zustände, etc. Virchow's *Archiv*, vol. xciv, p. 485.

Pflüger's *Archiv*, vol. xxiii, pp. 476–477.

the elimination of urea by four grammes a day. Oppenheim believes that the results obtained by Kerner were due simply to interference with the proteolytic action of the gastric and pancreatic juices, which the use of quinine certainly causes. Prior has shown, however, that such interference does not satisfactorily account for the unquestionable retarding influence of quinine on proteid metabolism.

Chittenden and Whitehouse,* working with cinchonidine sulphate, found that small doses of the drug diminished the excretion of urea and that large doses (fifty grains) diminished both urea and uric-acid, the latter out of proportion to the former.

It is probably safe to conclude that the various salts of quinine in moderate doses diminish uric-acid excretion out of proportion to the urea excretion, but it is greatly to be desired that more extended observations on quinine should be made.

Antipyrine.—Only a few of the observations that have been made on the influence of antipyrine on nitrogenous metabolism include the study of uric acid, and these observations give contradictory results. Thus Umbach,† experimenting both on himself and on a dog, found that four grammes of antipyrine in two days diminished slightly the excretion of total nitrogen, but had no perceptible effect on uric acid. Chittenden and Adams,‡ working on a healthy man, found that antipyrine in doses of thirty to sixty grains had a marked effect in checking the excretion of uric acid and

* Influence of Cinchonidine Sulphate on Metabolism. *Studies from the Laboratory of Phys. Chemistry*, Sheffield Scientific School of Yale College, 1884–'85.

† Ueber den Einfluss der Antipyrine auf die Stickstoffausscheidung Abstract in *Jahresbericht f. Thierchemie*, 1886, p. 418.

‡ The Influence of Urethane, Paraldehyde, Antipyrine, and Antifebrine on Proteid Metabolism. *Studies from the Laboratory of Phys. Chemistry*, 1887–'88.

urea, which were diminished nearly proportionately. More recent experiments by Kumajawa* are directly opposed in their results to those of Chittenden and Adams. This observer found that in a dog large doses of antipyrine (fifty-one grammes in sixteen days) produced no effect upon the excretion of urea, but increased the excretion of uric acid on the average to sixty-five per cent. above the normal. Obviously more work needs to be done before we can reach definitive conclusions regarding the effect of antipyrine upon uric-acid excretion.

Antifebrine.—The best work that has been done on the action of antifebrine on uric-acid excretion is that of Chittenden and Taylor.† It was found by these observers that, in a healthy man, doses of antifebrine, varying from six to forty grains a day, slightly increased the excretion of urea, but decidedly diminished that of uric acid. The conditions of the experiments were such in this case that there is good reason to think that doses of more than fifteen grains daily of antifebrine have a specific effect in lessening the excretion of uric acid. This effect of the drug is of considerable interest in connection with the fact that in chorea and migraine, both of which conditions are associated with an excessive elimination of uric acid, antifebrine has been used successfully as a therapeutic agent.

Thallin,‡ iron, lead, and mineral acids# are said to decrease uric-acid elimination; but the observations on which

* Virchow's *Archiv*, Bd. cxiii, p. 192.

† The Influence of Urethane, Paraldehyde, Antipyrine, and Antifebrine on Proteid Metabolism. *Loc. cit.*

‡ See Robin. *Berliner klin. Wochenschrift*, March, 1889.

Variations in the Excretion of Uric Acid and Urea produced by the Administration of Acids and Alkalies. A. Haig. *Journal of Physiology*. vol. viii, 1887.

this opinion is based are not of a character sufficiently serious to require consideration here.

6. The Excretion of Uric Acid in Disease.

We have seen that there is some lack of agreement on the part of writers regarding the influence of drugs upon uric-acid excretion. When we pass to the consideration of the relation of disease and uric-acid excretion we find an uncertainty about fundamental matters that opens our eyes anew to the imperfections of our knowledge.

Before referring to our own somewhat fragmentary work, which deals especially with nervous disease, we may advantageously review some of the more general aspects of the uric-acid question.

Not long since an English writer, Dr. Haig,* attempted to show that uric acid is in some way the cause of a long and almost suspiciously varied list of diseases, including gout, rheumatism, migraine, epilepsy, mental depression etc.

The idea of Dr. Haig is that these conditions are due, not to an increased formation of uric acid, but to its retention in the organism. Certain kinds of food, according to this view, render the blood less alkaline than normally, with the result that the uric acid formed is less perfectly dissolved than it should be, and is hence stored up in the tissues, instead of being removed from them.

This process of storing up continues until, as the result of an error or peculiarity in diet, the blood becomes more alkaline than before, and, in consequence of this increased alkalinity, the uric acid stored in the tissues is dissolved out into the blood. The blood (and consequently the urine) now contains a great excess of uric acid (uric acidæmia),

* *Uric Acid as a Factor in the Causation of Disease*, 1892, Blakiston.

and the patient suffers from uric-acid poisoning. This uric-acid poisoning is shown, in a general way, by a contraction of the peripheral arterioles, with increased blood-pressure and hard and slow pulse. The effects of the poison may, however, be shown in even a more striking way, as by an epileptic paroxysm, a migraine headache, or great mental depression, according to the particular predisposition of the patient. After a time the kidneys eliminate the excess of uric acid in the blood, and the blood ceases to acquire uric acid from the tissues, either because the tissues have no more uric acid to give up, or because the blood has grown less alkaline. When this elimination has occurred, the patient is once more relieved of his acute symptoms.

We believe this to be a fair general statement of the attitude of Dr. Haig regarding the relation of uric acid and disease. It will, however, repay us to examine his position somewhat critically.

Dr. Haig's views are based upon theoretical considerations and upon observation. Of the theoretical considerations on which these views rest, there are two which it is especially important to bear in mind. The first is that there is a varying condition of the uric-acid constituent of the blood, due to the varying alkalinity of the blood. The second is that the varying uric-acid excretion depends on corresponding variations in the *storage* of uric acid in the tissues, and not on changes in the formation of uric acid.

As to the first proposition, it may be said that, while it may safely be considered probable that the uric-acid content varies with the alkalinity of the blood, it must be admitted that there is no proof whatever that this is so. We know that uric acid is more soluble in highly than in weakly alkaline fluids, and there is nothing unreasonable in the supposition that a more alkaline blood would dissolve more uric acid, if it were accessible, than a less alkaline

blood. But, if there is really a definite relation between the uric-acid content and the alkalinity of the blood, it is a fact susceptible of direct demonstration such as we might very properly demand. Yet, so far as we are aware, we have not even satisfactory evidence that the uric-acid content of the blood does actually vary in the same individual. Neither have we satisfactory information about the varying alkalinity of the blood in the same individual in health and disease. The point we wish to make is that the proposition of which we are speaking may be and probably is true, but that it is, after all, a mere supposition at present. We may use it, if we choose, as a working hypothesis, but we must not forget, as Dr. Haig appears to do, that it has not been shown to be a fact.

The second proposition—namely, that the variations in uric-acid excretion depend on the varying storage of uric acid in the tissues and not upon changes in uric-acid production—appears to be without any foundation and seems improbable. It is difficult, in the first place, to suppose that uric acid is produced in any definite quantitative relation to urea, as held by Dr. Haig. Both urea and uric acid result from cell activities, which must be undergoing such continual changes in intensity as to make it in the highest degree improbable that they are produced under all circumstances of health and disease in even approximately the same relation.

There is likewise no evidence whatever that uric acid is stored in the tissues and redissolved when the blood grows more alkaline. The formation of urate-of-sodium tophi in gout has been regarded as positive evidence that in gout, at least, there is such a storage. But the fact of the formation of tophi is susceptible of explanation in another and perhaps more satisfactory way. According to this view, the local mechanical deposition of sodium urate de-

pends on local necrotic changes, which, in turn, depend on an excess of uric acid in the blood and not in the tissues.

We may now consider for a moment the character of Dr. Haig's observations on uric-acid excretion in disease. At the outset we are struck with the scantiness of the actual observations. On the urine of migraine a good many observations were made, but they were chiefly on one person and were made with an inaccurate method of estimating uric acid.* The urine in epilepsy was examined, so far as we can find, in only two or three cases.† Yet Dr. Haig has no hesitation in elaborating a uric-acid theory of epilepsy on the strength of his facts. And so it is with mental depression, suicide, gout, uræmia, Raynaud's disease, and a long list of conditions which Dr. Haig refers to uric acid poisoning. In each of these cases there is a huge superstructure of hypothesis upon a scarcely discernible basis of fact. We do not, however, wish to be understood as contemning Dr. Haig's work absolutely. It is only just to say that his writings contain many interesting suggestions, and that his observations, though obtained by an untrustworthy method, are probably not without value. Indeed, we may say that Dr. Haig's work upon the fluctuations of uric-acid excretion in migraine is of much interest, notwithstanding its deficiencies, and contains the best observations that have been made on this aspect of the disease. What we especially condemn in Dr. Haig's writings are the sweeping conclusions that are drawn from so small a store of facts; we do not object to his ideas as suggestions, but we take exception to them as conclusions in fact.

It is instructive to examine briefly the state of knowledge regarding two conditions which are of wide general

* Haycraft's method.

† *Uric Acid as a Factor in the Causation of Disease*, etc., 1892.

interest in connection with the uric-acid question—namely, uric-acid excretion in fever and in gout.

As regards uric acid in febrile conditions, it is generally assumed by authors that uric acid is excreted in excessive amount in fever from any cause, but especially in the case of fevers that are the result of conditions which produce embarrassed respiration (such as pneumonia, bronchitis, pleurisy with effusion, or pericarditis). There appears to be considerable doubt whether the uric-acid excretion is merely absolute or whether it is both absolute and relative as regards urea. Probably many of the statements that there is an increase of any kind in fever are based on the well-known separation of urates from fever urines. Scheube * states that in the case of pneumonia he found both an absolute and relative increase in uric acid. On the other hand, Bartels † has shown that in many cases of acute febrile disease the uric acid excreted was present in normal proportion to the urea. It is thus plain that our knowledge regarding the influence of fever is in a most unsatisfactory state. It has been thought that the supposed increase of uric acid in fever urines was due to the defective oxidation of nitrogenous substances, but there is no support for this view. Thus Senator ‡ and Nunyn and Riess # produced experimental dyspnœa in animals with a view to studying the effects of imperfect oxidation, but were unable to satisfy themselves that there was any alteration in uric-acid excretion. It has been often held that respiratory diseases in man cause increased uric-acid excretion, but there is no satisfactory evidence that this is so. The results that many writers have obtained are rendered worthless by the imper-

* *Archiv d. Heilk.*, 1876, xvii, p. 185.
† Von Ziemssen's *Handbuch*, ix.
‡ Virchow's *Archiv*, 42, p. 1.
# Dubois-Reymond's *Arch.*, 1869, p. 381.

fections of their methods and their ignoring of the influence of diet. Bunge * makes a very positive statement that in diseases of the respiratory organs the uric-acid excretion varies, in its relation to the excreted urea, within limits that are to be unhesitatingly considered normal. It is an interesting fact in this connection that in birds, whose respiration is the most active of any class of animals, nearly all the nitrogen excreted is in the form of uric acid. Indeed, nitrogen may be introduced into the body of a bird in almost any form—as urea,† as leucine, as glycocoll, as ammonium carbonate,‡ or as hypoxanthin #—and the nitrogen reappears in the urine as uric acid and not as urea. It must be owned, however, that we should not allow these facts, whose significance is not clear, to weigh too much with us in the consideration of the relation between defective oxidation of nitrogenous tissues and excessive uric-acid excretion. We may, nevertheless, conclude that there is no good reason for referring excessive uric-acid excretion, in febrile or other conditions, to defective oxidation.

One might reasonably expect that in the case of gout there should be some well-established facts regarding the uric-acid excretion, since it is in this connection that most has been said and written about uric acid as a cause of disease. But when we come to examine the actual observations on the occurrence of uric acid in the urine in gout we find that most of them are of an unsatisfactory nature. According to Garrod, whose views have been widely accepted, there is an increase of uric acid in the blood during the

* *Lehrbuch*, p. 301.

† Meyer and Jaffé. *Ber. d. deutsch. chem. Ges.*, Bd. 10, S. 1930, 1877.

‡ Schröder. *Zeit. f. physiol. Chemie*, 1878.

W. von Mach. *Arch. f. exper. Path. u. Pharmak.*, Bd. 24, S. 389, 1888.

paroxysmal period, due either to its over-production or defective elimination. For a long time this opinion was based entirely on the results of the well-known thread experiment, which is said by recent writers to be unreliable. Von Jaksch,* however, has recently shown, by actual analysis, that there is an excessive accumulation of uric acid in the blood in gout. Coincident with this increase in the blood there occurs, according to Garrod, a decided diminution in the excretion of uric acid by the urine. Recently Ebstein † has attacked this view of Garrod and stated that it is in the highest degree improbable that there is any diminution in the uric acid excreted. He refers the results of Garrod to the use of imperfect methods. It certainly is difficult to believe that an excess of uric acid in the blood can be associated with a diminution of it in the urine. It is much more probable that whenever the blood contains an excess of uric acid there is a prompt increase in the elimination of uric acid by the kidney.

Probably the most satisfactory work that has been done in late years on uric acid in gout is that of Pfeiffer.‡ According to this observer, there is a decided diminution in the excretion of uric acid in all cases of gout, except during a paroxysm. This diminution he considers characteristic of gout, even in its earliest stages. When the cachexia of gout develops there is also a great diminution in the excretion of urea, and we are not clear whether or not, according to Pfeiffer, there is then merely an absolute diminution of uric acid or a relative diminution also.

During a paroxysm of gout there is regularly, according to Pfeiffer's view, an increase in uric-acid excretion, at least as compared with the excretion before and after the

* *Deutsch. med. Woch.*, 1891.

† *Verh. d. Congr. f. innere Med.*, 1889, viii, p. 133.

‡ *Ibid.*

paroxysm. In some cases the diminution which regularly precedes the attack may persist during the first and second day of the attack, but in every case there is, contrary to Garrod's view, an increase during the paroxysm. Pfeiffer believes that in gout there is not necessarily any increased *formation* of uric acid, but rather a retention of it in the tissues and body fluids, owing to its being present in an insoluble form. We shall not, however, concern ourselves further with this question, which is largely one of theory. The observations of Pfeiffer appear to be well made, and his conclusions are consistent with what we know about uric-acid excretion. The one criticism it is necessary to offer on his work is that he employed a notoriously poor method of determining uric acid. We can not say to what extent this deficiency may have impaired the value of his results.

We have referred to the state of our knowledge as to uric-acid excretion in gout and in fever partly to illustrate the uncertainty that still exists regarding such common conditions. How little we actually have known until recently about uric-acid excretion in disease is shown by the remark of Bunge, in his recent work,* that up to the present time (1889) there is only one disease in which it has been positively shown that there is an excessive excretion of uric acid—namely, leucæmia. But at the present time this statement would scarcely hold, for we have proof that there are several functional forms of nervous disease in which uric-acid excretion is abnormally large. We may pass to the consideration of these conditions.

Our own work refers especially to chorea, epilepsy, neurasthenia, and migraine, and we shall confine our attention especially to these forms of disease.

So far as we are aware, no observations have hitherto been made on uric acid in chorea, and our own work is not

* *Lehrbuch*, 1889, p. 301.

so extensive as could be desired. In four cases of chorea in which we have studied the urine there was a continuously excessive excretion of uric acid. This excess appeared to be proportional to the severity of the choreic movements, and grew less under the influence of treatment and in proportion as this was effective. We shall elsewhere give our data in full.

Not long since Haig advanced the proposition that epilepsy and certain kinds of headache, especially migraine, depend on temporary uric acidæmia. Haig's claim is that the epileptic paroxysm is preceded by a diminished excretion of uric acid, that the paroxysm itself coincides with an excessive excretion of uric acid, and that after the paroxysm the excretion falls quietly back to the normal.

This view appears to rest chiefly on the fact that in one case of epilepsy, recorded in the *Neurologisches Centralblatt* for 1888, Haig observed a diminution of the ratio to 1 to 50 (which he considers abnormal, 1 to 33 being his normal) before paroxysms, and of 1 to 20 immediately after them. Haig states that he has investigated other cases, but does not give figures that are satisfactory. He appears to recognize in some degree the insufficiency of the facts on which he bases his hypothesis, for he says that he would have liked to examine a large number of cases, but found the difficulties too great. Being, as he admits, unable to extend his observations to his satisfaction, he abandons his investigations and retreats from fact to speculation. "I now look upon many other signs and symptoms," says he, "as more or less satisfactory evidence of uric-acid causation."

A similar indication of the insecurity of Dr. Haig's position is that he constantly attempts to support it by leaning on purely clinical considerations. He thinks, for example, that the uric-acid theory of epilepsy must be correct because there is a close clinical relationship between

epilepsy and migraine, and he believes that he has shown migraine to be a "uric-acid headache."

We have made an extended series of observations on the state of uric-acid excretion in epilepsy. The detailed presentation of these observations and the conclusions that follow from them we propose to defer to another occasion. We may, however, say here that we have as yet obtained no grounds for the view that the *grand-mal* paroxysm of idiopathic epilepsy is regularly or even usually preceded by a diminished uric-acid excretion. On the other hand, our results support the view of Haig to the extent that we find the paroxysm to be usually succeeded by an increase in the uric acid of the urine. In many cases the increase is greatest on the second day after the seizure.

This latter fact suggests that the increase in uric acid is the result of conditions that are associated with, and perhaps determine, the paroxysm, and that this increase is not itself a cause.

We have made some observations which suggest that the uric-acid factor is of more significance in cases of *petit mal* than in cases of *grand mal* of idiopathic type. Thus, while the *grand-mal* cases in general have shown merely an increased excretion of uric acid after the paroxysm, the *petit-mal* cases have shown a large and persistent excess in the uric acid of the urine. That this excess has been in some degree related to the *petit-mal* seizures in three cases which we have examined repeatedly, was shown by the cessation or reduction in frequency of the seizures by the use of a diet which has lessened uric-acid elimination. This suggestion is further based on the repeated examination of the urine in seventeen cases of *grand mal*, many of which were placed at our disposal by the courtesy of Dr. Fisher. Up to the present time we have made one hundred and fifty-six determinations of uric acid in these cases of epilepsy.

Analysis of the urine from nine cases of pronounced neurasthenia showed in each instance but one an excess of uric acid. In this case the ratio was on the border line. In four of the cases the neurasthenic symptoms were referable directly to sexual excess. As a group these cases show nothing distinctive. A marked feature in some of the neurasthenic cases was a tendency to rather sudden variations in the ratio of uric acid and urea.

Table showing Uric-acid Excretion in Neurasthenia.

No. of case.	Symptoms.	Quantity.	Sp. gr.	Chlorine.	P_2O_5.	Urea.	Uric acid.	Ratio of uric acid to urea.
		C. c.					Grm.	
1	Headache,	1,585	1·024½	12·398	3·312	42·671	·789	1 : 54
"	general debility, loss of memory.	1,310	1·022	8·945	2·177	29·977	·654	1 : 45·8
"		1,235	1·026	9·813	2·678	35·742	·844	1 : 42·3
2	Pressure sensation on vertex, mental depression.	1,670	1·017	5·610	2·103	29·893	·731	1 : 40·9
"		1,305	1·016½	.....	.....	25·839	·698	1 : 37·1
3	....	720	1·019½	.....	1·170	14·832	·326	1 : 45·5
"	.....	2,654	1·020	.....	4·099	41·400	1·067	1 : 38·8
"	.....	1,818	1·021½	.....	.....	38·905	·773	1 : 50·3
"	.....	1,907	1·022½	.....	4·238	46·340	1·100	1 : 42·1
"	.....	2,010	1·023½	.....	4·880	47·838	1·257	1 : 38
"	.....	2,277	1·020	.....	3·819	47·435	1·100	1 : 43
4	Headache,	1,950	1·011½	3·631	2·619	23·999	·637	1 : 37·6
"	mental depression.	1,950	1·011½	3·510	2·6775	22·637	·493	1 : 46
"		2,070	1·09½	4·627	2·142	22·689	·568	1 : 39·7
5	Headache, debility.	840	1·018	5·319	·727	11·873	·4074	1 : 29·1
6	Hypochondriasis.	1,150	1·026	4·7118	2·586	35·162	·9953	1 : 35·3
7	Headache,	1,005	1·024	6·239	2·150	30·148	·669	1 : 45
"	hypochondriasis, debility.	1,000	1·024	6·338	2·030	25·768	·558	1 : 46·7
8	Irritability, debility.	650	1·030	4·578	2·069	24·393	·648	1 : 37·5
9	Irritability, depression.	1,640	1·027½	12·1	3·431	48·543	1·417	1 : 34·2

In all the cases that are tabulated below, organic disease of every kind was so far as possible excluded. The influence of alcohol was also barred out.

Our observations on migraine are few in number. In one case two paroxysms were studied; in another case only one paroxysm was studied. In each paroxysm a considerable excess in the excretion of uric acid was observed immediately *after* the period of headache. No diminution of uric acid was found in the samples of urine passed immediately before the period of headache.

In two cases of paroxysmal vomiting in children we have made observations which we believe to be unique. Both the cases were under the care of Dr. L. E. Holt, from whom the histories were obtained. The first case is that of a boy, aged seven, who, since his third year, has had occasional periods of persistent vomiting, usually with headache and some rise in temperature. The paroxysms could not be referred to any intelligible cause. In the intervals the boy enjoys what is apparently perfect health. A twenty-four-hour sample of urine obtained in an interval of health showed a ratio of uric acid to urea of 1 to 56—*i. e.*, a normal relation. A twenty-four-hour sample from the first day of a period of uncontrollable and repeated vomiting showed a ratio of uric acid to urea of 1 to 159. During the second day of the attack the relation was 1 to 134. On the third day the vomiting ceased and all the symptoms cleared up. The ratio on this day was 1 to 50, but it is certain that this relation is too low, as only the uric acid in the sediment was included in the analysis.

Fourteen weeks after this attack the patient had another. On the first day of the seizure the ratio was 1 to 164·8; on the second day it was 1 to 157. On the following day, as the symptoms wore away, the ratio was 1 to 24·9. We have in this case an example of an acute parox-

ysmal disorder, characterized especially by persistent vomiting, in which the attacks coincide in time with a very great diminution in the excretion of uric acid and are followed by a period in which its excretion is increased.

The second case which we have to relate belongs apparently to the same clinical type. In this case the patient, a healthy girl, aged four years and a half, developed symptoms which during two days justified a suspicion of tubercular meningitis. There were present the following conditions in the course of four days: persistent vomiting, obstinate constipation, marked retraction of the abdomen, irregular breathing and pulse, and, on the first and third days, slight fever. The urine of the first and fifth days was studied.

On the first day the ratio of uric acid to urea was 1 to 83·5—that is, distinctly low. On the fifth day it was 1 to 21—that is, very high. A normal specimen obtained some time later gave a ratio of 1 to 42·1. It is to be regretted that the examination did not extend over the entire time of the attack in this case, but the results, such as they are, are suggestive. A detailed presentation of these cases is given on the following page.

We have touched upon some of the aspects of the uric-acid question which relate to clinical medicine. We have shown that in the investigation of a particular case it is necessary to study especially the quantitative relation that exists between urea and uric acid, for we can place little reliance on the totals themselves, which vary with conditions which we can not hope to control in clinical work. Since, as we have further shown, the variations in this relation are slight in the same individual in health, it follows that any considerable derangement of the normal relation is readily appreciable. The degree and persistency of any derangement in the relation may afford us a valuable index

Table illustrating the State of Uric-acid Excretion in Two Cases of Persistent Vomiting.

		Case I.	Ratio of uric acid to urea.
Urine before paroxysm (normal).		Urea, 13·606 grm.; Uric acid, ·2515 "	1 : 54·2
1st paroxysm.	First day of paroxysm.....	Urea, 17·249 grm.; Uric acid, ·11 "	1 : 156·9
	Second day of paroxysm...	Urea, 12·023 grm.; Uric acid, ·0912 "	1 : 131·8
	Directly following paroxysm	Urea, 11·713 grm.; Uric acid, ·2345 "	1 : 50
Urine after paroxysm (normal)..		Urea, 15·040 grm.; Uric acid, ·2827 "	1 : 53·1
2d paroxysm.	First day of paroxysm.....	Urea, 12·576 grm.; Uric acid, ·0763 "	1 : 164·8
	Second day of paroxysm...	Urea, 13·824 grm.; Uric acid, ·088 "	1 : 157
	Directly following paroxysm	Urea, 21·07 grm.; Uric acid, ·839 "	1 : 24·9

	Case II.	
First day of paroxysm.....	Urea, 12·285 grm.; Uric acid, ·147 "	1 : 83·5
Fifth day of paroxysm.....	Urea, 10·428 grm.; Uric acid, ·495 "	1 : 21
After paroxysm (normal).....	Urea, Uric acid,	1 : 42·1

of the severity of condition with which we have to deal —a better index, perhaps, in some cases than the symptoms themselves, which may, as in the case of neurasthenia, be chiefly subjective. In many cases the variations in the quantitative relation, as the morbid condition progresses, may be advantageously noted with a view to watching the effects of treatment and of obtaining in this way facts for the establishment of a rational prognosis. We have ourselves been able to use some of our observations to advantage for this purpose.

But while we have thus dwelt upon some of the more practical relations of uric acid in health and disease, we

have ignored the question which, of all the interrogatives of the uric-acid problem, is of the greatest interest. That question is, What is the significance of the excessive excretion of uric acid which is a concomitant of disease? Or, in other words, What is the relation of this uric acid excess to the cause of the morbid process? We doubt whether it is possible, at the present time, to give a satisfactory reply to this query, but shall endeavor to show, though it be but imperfectly, what are the considerations that should weigh most with us in trying to approach it.

The first fact to bear in mind in this connection is that excessive uric-acid excretion is a condition that is observed in a considerable number of clinical conditions. As we have already seen, it occurs in neurasthenic states, in migraine, in epilepsy, in chorea, in fever, in leukæmia, and as the result of the use of considerable quantities of alcohol. There can be no doubt that this excessive excretion is a common condition, and there is reason to think that a more extended study of the subject than has yet been made would show it to occur with greater frequency than has ever been suspected, especially as a consequence of disorders of digestion. Another fact of importance is that the conditions which have been enumerated as being associated with uric-acid excess differ widely in their clinical characters. It needs no argument to emphasize the clinical contrast between chorea and leukæmia, or that between an acute febrile and a neurasthenic state. But the fact that these conditions (so widely different that their comparison is amusing) have in common the excessive excretion of uric acid, leads us at once to the conclusion that this excess can not reasonably be regarded as the *specific* cause of any one of the numerous morbid states of which such excess is characteristic. It is certainly true that the conditions we have named differ as widely in their ætiology, so far as we

understand it, as do the clinical types themselves. How, then, shall we interpret the important condition which these different types have in common? Our view of the matter is as follows:

Uric acid, like urea, is an end-product of nitrogenous metabolism. There seems to be no evidence to show that the formation of uric acid is a necessary precursor to the formation of urea. Such evidence as there is points to the idea that both these substances are the consequences of a more or less lengthy and varied series of metabolic changes, and that the formation of uric acid is expressive of merely a slight divergence from the process that ends with the production of urea.

An increase in the formation of uric acid, such as to make the quantity in the urine bear a higher ratio to the urea of the urine, is to be regarded as the result of a derangement in the development of the chain of nitrogen-holding substances that make their successive appearance for a short period of time between the commencement of digestion and the completion of destructive metabolism. What these substances are and how they are related to one another is still largely unknown to us, but there seems nothing unreasonable in the view that in conditions of disease the early links in the chain may differ from those that belong to health, and may possibly present a considerable divergence among themselves in different morbid processes.

But whatever may be the character of the original disturbance or of the morbid substances concerned in it, as destructive metabolism progresses there are only a few substances, so far as we know, through which these concomitants of deranged nitrogenous metabolism may be eliminated from the body. Of these, one of the most important appears to be uric acid.

According to this view, then, the increased excretion of

uric acid that is met with in disease might be an *effect* of numerous different derangements in nitrogenous metabolism. We believe that this suggestion harmonizes with the fact that uric-acid increase may be brought about by so many different nutritional disorders. In this excessive excretion we should be dealing with the *result* and probably not with the *cause* of disease. Excessive uric-acid formation, in other words, is a terminal process that may result from different and perhaps numerous different initial morbid nutritive conditions. The fact that we can not now point out what these derangements consist in or with what poisonous substances they are identified, does not make less reasonable the view we have ventured to suggest.

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